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The Study and Manipulation of Experimental Autoimmune Disease Using T Lymphocyte Lines

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Autoimmune diseases include entities of varied clinical expression such as juvenile onset diabetes mellitus, rheumatoid arthritis, multiple sclerosis, and thyroiditis. Nevertheless, these autoimmune diseases have a common origin; they are caused by clones of lymphocytes that specially attack the individual's own body components. To study autoimmune processes, we have isolated and grown as long-term cell lines the T lymphocytes that mediate several different experimental autoimmune diseases in rats or mice. These cell lines have increased our understanding of pathogenesis, but perhaps more importantly, it appears that suitably attenuated lines can be used to immunize the individual animal against its own autoimmune cells. Thus, autoimmune cells can be used as vaccines to prevent or treat the autoimmune process.

The object of this article is to review salient findings in studies of animal models of autoimmune diseases in which we have used long-term cultured lines and clones of T lymphocytes to study and manipulate the diseases. I shall introduce the disease models, discuss their contribution to our understanding of pathogenesis and resistance to disease, and briefly comment on the possible application of the new information to problems in human autoimmunity.

Our use of autoimmune T cell lines to study autoimmune diseases is based on an idea of demonstrated usefulness in infectious diseases; pathogenesis and control of disease can be explored most easily when the etiologic agent is available for study and manipulation in pure culture. Autoimmune diseases patently differ from infectious diseases in that the etiologic agents are the individuals' own lymphocytes and not invading microbes. Nevertheless, we were attracted by the possibility that, similar to pathogenic bacteria, autoimmune effector T lymphocytes might be grown in pure culture in vitro and used to advantage both to investigate how such cells cause disease and to develop new approaches to prevention or therapy by vaccination [1].

EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE)

EAE can be induced in a variety of species—rats, mice, guinea pigs, rabbits, dogs, monkeys, or humans—by immunization to white matter of the central nervous system (CNS) in a suitable adjuvant such as complete Freund's adjuvant (CFA). The disease is characterized clinically by acute paralysis and histologically by mononuclear cell infiltrates around blood vessels in the white matter of the CNS [2]. The critical antigen responsible for EAE is the basic protein of myelin (BP) [3]. It is interesting that different portions of the BP molecule are encephalitogenic for the various species. For example, the major encephalitogenic fragment of bovine BP for guinea pigs is a nonapeptide composed of residues 114–122 of the molecule [4], while for rats the major encephalitogen is within the 68–88 fragment of guinea pig BP [5]. Bovine BP is a relatively weak encephalitogen for rats and its encephalitogenic epitope is not in the 68–88 region [6].

EAE-induced using purified BP or fragments of BP is usually an acute monophasic disease and does not often manifest demyelination. Chronic or relapsing EAE with demyelination can be obtained in certain species by using particular procedures of immunization with whole white matter rather than with BP [7]. Thus, the clinical manifestations of EAE can be influenced by the mixture of antigens and the mode of immunization. Once rats or other animals recover from acute EAE, they acquire resistance to subsequent attempts to produce additional bouts of EAE by active immunization with BP [8].

EAE was the first autoimmune disease to be produced by lines of T lymphocytes. Ben-Nun and his associates developed T lymphocyte lines selected for their responses to BP and found that a single i.v. inoculation of such cells (10^5-10^6) into naive syngeneic Lewis rats led to the clinical and histological lesions of EAE [9,10]. Instead of a latency period of 11 or 12 days for expression of active EAE, the latency of disease induced by anti-BP line cells was inversely proportional to the number of line cells inoculated and could be as short as 2 days after a dose of around 10^7 cells. Similar to active EAE, EAE mediated by line cells was acute and most rats recovered spontaneously within 4–6 days. Only intact, activated anti-BP line cells induced EAE; cells treated by irradiation or mitomycin C, or cells specific for other antigens did not produce disease [11].

It was demonstrated that the anti-BP EAE effector line cells were not cytotoxic to BP-pulsed antigen presenting cells (APC) in vitro [12], although anti-BP cytotoxic T cells could be detected readily in immunized rats as they had in guinea pigs [13]. In addition to EAE, the line cells could also transfer to recipients' delayed hypersensitivity skin reactions to BP [12]. Therefore, the cells functioned as delayed hypersensitivity T lymphocytes, and showed the surface markers of helper or delayed hypersensitivity T lymphocytes [10]. Expression of EAE did not appear to require the recruitment of radiosensitive cells in the recipients as severe EAE developed in rats irradiated with 750 R.

EXPERIMENTAL AUTOIMMUNE THYROIDITIS (EAT)

EAT, manifested by inflammatory cell infiltration of the thyroid gland is induced in mice by immunizing them with mouse thyroglobulin (Tg) in CFA [14]. Antibodies to Tg are produced by mice of almost all H-2 genotypes, but some H-2 haplotypes such as H-2^b express a low incidence of EAT (about

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Abbreviations:
AA: adjuvant arthritis
BP: basic protein of myelin
CFA: complete Freund's adjuvant
EAE: experimental autoimmune encephalomyelitis
EAT: experimental autoimmune thyroiditis
MHC: major histocompatibility complex
MT: *Mycobacterium tubercolosis*
PPD: purified protein derivative
Tg: thyroglobulin

20%) while others such as H-2^k express a high incidence (about 80%). Thus, H-2 high and low responder phenotypes relate to the incidence of inflammation in the gland and not to the titer of Tg antibodies. Maron and Cohen mapped a critical EAT gene to H-2K [15].

Ruth Maron, Rachel Zerubavel, and their associates developed lines of mouse T lymphocytes [16] by priming mice with Tg/CFA and using Tg to select lymphocytes according to the method developed by Ben-Nun and Cohen [10]. A single intravenous inoculation of around 10^5 activated anti-Tg line cells was sufficient to induce EAT in naive mice, irradiated (550 R) mice, or thymusless nude mice. Large numbers of line cells (about 10^6) produced disease in some recipients within 1 day and in all recipients within 3 days of inoculation. The thyroiditis was markedly more severe than that seen in active EAT and ran a subacute course, lasting for many weeks. EAT was mediated by line cells in the absence of Tg antibodies, providing confirmation of the conclusion that T lymphocytes unaided by antibodies could produce EAT [16].

ADJUVANT ARTHRITIS (AA)

AA is a chronic inflammation of the joints inducible in certain strains of rats that is similar pathologically to aspects of rheumatoid or other forms of immune arthritis in humans [17,18]. Unlike other models of experimental autoimmunity, AA is induced not by immunization to a defined self-antigen, but by immunization with CFA or with fractions of *Mycobacterium tuberculosis* (MT) organisms. AA was suspected to be an autoimmune disease because it could be transferred to native rats by lymphocytes from rats with AA [19]. Some workers suggested that collagen type II was the self-antigen target of immune attack in AA [20], while others have challenged this notion [21].

Development of arthritogenic lines of T lymphocytes in AA was complicated by the obscurity of the putative autoantigen; there was simply no self-antigen known that could be used to select the relevant T lymphocytes in vitro. Joseph Holoshitz and his colleagues solved this problem by using ground MT as the stimulating antigen in cell culture. Although we did not know the identify of the arthritogenic antigen, we reasoned that the receptors of the arthritogenic lymphocytes themselves should recognize the critical antigen from among the many irrelevant MT antigens. Be that as it may, arthritogenic lines of T lymphocytes were generated using ground MT [22].

Unlike the EAE and EAT lines that were capable of inducing disease in naive recipients, the arthritogenic lines produced disease only in irradiated recipient rats (750 R). Line-mediated AA required inoculation of about 2×10^7 line cells, another marked difference from the EAE and EAT models that were inducible with 100-fold fewer cells. The synovia of the joints constitutes a large area for attack by the line cells compared to the focal targets provided by the CNS and thyroid and consequently more line cells might be required to produce clinical arthritis. In any case, the line cells produced a subacute synovitis with the histologic picture of AA beginning 5–7 days after inoculation and lasting up to 1 month.

We are now using arthritogenic clones as tools to identify the critical arthritogenic self-antigens in AA. The first line, A2, showed a small but significant degree of proliferative activity in vitro to collagen type II, suggesting that collagen type II might be the target of disease [22]. However, we have now cloned the A2 line and have isolated a highly arthritogenic subline, A2b that demonstrates no reactivity at all to collagen type II [23]. Thus, it is unlikely that collagen type II is the arthritogenic target antigen. Recent studies using the A2b clone suggest that AA is caused by cross-reactivity between an antigen of MT and proteoglycans of joint cartilage (W. van Eden and J. Holoshitz). Thus, relevant T lymphocyte clones can be raised without using purified antigens and such clones can then be used to identify the critical antigen.

COVERT AUTOIMMUNITY

The use of line technology to isolate and expand a limited number of T lymphocytes from the lymphoid organs of rats and mice has made it possible to define a *carrier state of autoimmunity,* the presence of potential EAE effector T lymphocytes residing peacefully in the bodies of seemingly healthy animals. We have raised anti-BP effector T lymphocytes from the thymuses of rats that had recovered from line mediated EAE [24] and from lymphoid organs of rats that had recovered from active EAE, or that had been inoculated with BP in incomplete Freund's adjuvant [8]. Moreover, genetically-resistant PVG strain rats were found to be capable of generating and were responsive to anti-BP EAE effector T lymphocytes [25]. We had originally reported that EAE-resistant BN rats developed anti-BP T lymphocytes, but that these cells were not pathogenic [25]. However, we have now isolated pathogenic anti-BP T lymphocyte lines from BN rats. Thus, genetic resistance to EAE is compatible with the generation and carriage of covert autoimmune effector T lymphocytes.

We have also succeeded in obtaining thyroiditogenic lines of anti-Tg-T lymphocytes from H-2^b strains of mice that are genetically resistant to EAT (unpublished data). These show major histocompatibility complex (MHC) restriction in that they produce disease in low-responder H-2^b mice but not in high-responder H-2^k mice. Thus, low responder mice possess thyroiditogenic T lymphocytes and these T lymphocytes are restricted to low-responder H-2 products.

The finding of autoimmune effector T lymphocytes in seemingly healty animals implies the existence of control mechanisms, among them genetic, that regulate the expression of these potentially virulent cells. I shall return to the question of resistance to autoimmunity in the section on vaccination.

MIGRATION OF AUTOIMMUNE T CELLS IN VIVO

The production of lesions by autoimmune T lymphocytes in specific organs requires that the effector cells recognize the target organ as they circulate in the blood and lymph, exit from the vascular compartment, and atack the organ in vivo. Experiments were undertaken by Naparstek and others to investigate the homing of anti-BP T lymphocyte line cells to the CNS and the biochemical machinery that might be used by T lymphocytes to penetrate blood vessels at the site of antigen. We found that ^{51}Cr-labeled anti-BP T lymphocytes were rapidly cleared from the blood and the majority lodged in the liver (85%) and spleen (10%). One or two days before the onset of clinical EAE, about 2% of the injected cells were found in the CNS [11]. Line cells of other antigenic specificities were never found to accumulate in the CNS, even during EAE. Thus, the onset of clinical EAE was heralded by the accumulation in the CNS of a small fraction of the administered anti-BP line cells.

We were surprised to find that about 1% of anti-BP line cells accumulated in the thymus [24]. These autoimmune T cells were found to persist for months in the thymuses of rats that had spontaneously recovered from EAE, and could be isolated, cultured in vitro, and shown to induce disease in new recipients. In actively induced EAE, we could also detect anti-BP effector T lymphocytes in the thymuses of recovered rats [8]. Thus, in addition to being a seat of cell differentiation, the thymus was found to be a repository of mature T lymphocytes returning from the periphery.

Persistence of autoimmune T cells in the thymus is another example of the carrier state of autoimmunity. Presumably, activation of persisting cells could be responsible for recurrent attacks of autoimmune disease.

Homing of anti-BP T cells to the CNS implied that the cells must have the means of recognizing the CNS when they course through it in the blood and penetrating the vessel wall to enter the substance of the CNS. A candidate for such a mechanism is a specific enzyme, an endoglycosidase, that digests the he-

paran sulfate component of the vascular basement membrane. We found that activated effector T lymphocytes, similar to metastatic tumor cells, express such an enzyme in vitro [26]. Moreover, the presence of the BP antigen at the basement membrane led to a 5-fold increase in the enzyme. Thus, it is conceivable that BP leaking from the CNS can be recognized in the walls of the CNS blood vessels by anti-BP T lymphocytes and that this recognition induces expression of an enzyme needed by the T lymphocytes to penetrate into the target tissue [26].

PATHOGENIC MECHANISM OF DISEASE

Once autoimmune T cells enter the target tissue, how do they cause damage? We have observed 2 different mechanisms that could account for paralysis in EAE: by-stander inflammation and inhibition of nerve conduction.

Bystander Inflammation

It was reported that inflammation of the CNS could be produced in animals with delayed hypersensitivity to purified protein derivate of MT (PPD) by injecting the PPD antigen into the CNS [27]. We have now confirmed and extended this using T cell lines specific for a variety of antigens. For example, anti-PPD line T cells introduced i.v. were induced into entering the CNS by inoculating rats intracerebrally with PPD [12]. Entry of the cells was associated with paralysis and EAE-like lesions. Arthritis or hepatitis was produced by injecting the PPD antigen into the joints or liver, respectively. Similar findings were obtained with other foreign antigens and antigen-specific line cells. Thus, inflammation that was similar to autoimmunity could be induced using exogenous antigens in animals with T lymphocytes specific for the antigens. The T lymphocytes responsible for this bystander inflammation were delayed-type hypersensitivity cells [12].

Paralysis In Vitro

As the clinical course of EAE cannot always be correlated with the presence or severity of cellular infiltrates in the CNS, we suspected that processes in addition to delayed hypersensitivity reactions might play a role in the pathogenesis of EAE. Together with Yosef Yarom, an electrophysiologist, we tested the effects of line cells on nerve conduction in vitro [28]. We found that the presence of activated anti-BP T cells inhibited nerve conduction in syngeneic optic nerves, but not in syngeneic peripheral nerves, or in allogeneic optic nerves. Line cells recognizing antigens other than BP had no effect. Moreover, inhibition of nerve conduction was reversible and removing the anti-BP T lymphocytes led to recovery of nerve function. Hence, anti-BP line cells seemed to exert an immunologically specific, but reversible, blockade of nerve conduction. The requirement for syngeneic optic nerve was compatible with associative recognition of BP together with self-MHC at the level of the target nerve.

VACCINATION AGAINST AUTOIMMUNITY

The above findings suggested that the various line cells were etiologic agents of EAE, EAT, or AA. Taking a cue for infectious diseases, could these autoimmune T lymphocytes be used as agents for vaccination to induce resistance or treat disease without causing disease.

EAE

Anti-BP line cells were treated with irradiation or mitomycin C to attenuate their virulence and the cells were inoculated into syngeneic rats. We found that a single i.v. inoculation of about 10^6 or more attenuated line cells vaccinated about ⅔ of recipients against active EAE [29]. We initially observed that vaccination was effective in preventing active EAE, but did not inhibit EAE mediated by anti-BP T lymphocyte lines [30]. However, we have now discovered that resistance to line mediated EAE may be obtained by repeated vaccination (unpublished data).

Anti-BP lines that recognize different antigenic determinants on the BP molecule could be used to vaccinate only against EAE induced by active immunization to that specific determinant [31]. Thus, the receptor specificity of the anti-BP line cells directed the fine specificity of the vaccination effect, a finding compatible with an antireceptor (anti-idiotypic) mechanism of vaccination.

EAT

A single inoculation of 3×10^6 irradiated anti-Tg cells vaccinated syngeneic mice, not only against active EAT induced by Tg/CFA, but also protected them from EAT mediated subsequently by passive transfer of the intact line cells [16]. Although protection against thyroid inflammation was complete, the vaccinated mice produced high titers of Tg antibodies in response to active immunization. Thus, vaccination was selective in suppressing the EAT effector cells, but left untouched the Tg specific helper T cells and B lymphocytes needed for induction of antibody production. This selectivity could be explained by anti-idiotypic mechanism capable of distinguishing between effector and helper T lymphocytes that might interact with different antigenic determinants on Tg.

AA

We found that a single i.v. inoculation of A2 line cells protected all recipient rats against active AA induced by CFA from 2 weeks to at least 6 months later [22,23]. Because unirradiated recipients are refractory to line-mediated arthritis, we could induce vaccination in unirradiated rats using untreated line cells.

A useful feature of active AA is its chronicity, lasting for weeks rather than days as does active EAE. We therefore were able to test whether A2 line cells, in addition to prevention, could be used to treat active AA after its clinical onset. Rats in which AA had been induced by CFA 16 days earlier, showed rapid regression of arthritis following administration of A2 line cells compared to controls (manuscript in preparation). Thus autoimmune T lymphocyte line cells can be used as therapeutic agents and not only as vaccines.

Resistance to AA could be transferred from vaccinated rats using their thymus cells. This suggests that resistance induced by vaccination was immunological and probably involved T lymphocytes (J. Holoshitz, A. Matitiau, I. R. Cohen).

Recently, we isolated a clone of line A2 that has no arthritogenicity, but administration of the intact clone to rats makes them resistant to subsequent atempts to induce AA. The clone could also be used to treat ongoing AA (unpublished data). The protective clone seems to recognize a different antigen than does the A2b effector clone (unpublished data). These findings suggest the possibility that the protective clone may work by inducing suppressor cells that inhibit the disease process. The protective clone, similar to the arthritogenic A2b clone, has the surface markers of helper T cells. Thus, the suppressor clone may be what is called a suppressor-inducer cell.

These findings suggest that protection, in addition to an antireceptor or anti-idiotypic mechanism, may involve activation of suppressor cells. Thus, it is possible that more than one protective mechanism can be mediated or induced by T lymphocyte lines or clones. Be that as it may, it is clear that long-term cultures of autoimmune T lymphocytes provide a new approach toward the control of autoimmune disease, at least in laboratory animals [1].

PROSPECTS

Human diseases thought to involve autoimmunity include multiple sclerosis, rheumatoid and similar types of arthritis, insulin-dependent diabetes mellitus, thyroiditis, myasthenia gravis, systemic lupus erythematosus, and some skin diseases. Given our success in preventing or treating 3 experimental autoimmune diseases, what are the prospects for clinical use of T lymphocyte line cells in human autoimmunity?

It may be claimed that clinical autoimmunity differs fundamentally from our experimental models in that the clinical diseases are spontaneous while the experimental models we study are induced. Is there any reason to hope that processes effective in modifying artificially induced autoimmunity could be effective in modifying spontaneous diseases in which premeditated immunization plays no role? This is a weighty question. However, the term spontaneous may be merely a cover for our ignorance about the factors that actually trigger human autoimmune diseases. We say a disease develops spontaneously when we don't understand how the process is initiated. If disease is the outcome of an interaction of the individual with his or her environment, then factors in the environment may be viewed as inducers of the disease. When the critical environmental factors are unknown, we say the disease is spontaneous. Disease, similar to most biological happenings, is the outcome of an interaction between an individual genome and forces in the environment. The term spontaneous places the brunt of the blame on the genome while the term induced incriminates the environment. Human and experimental models involve both the genome and the environment. The 3 experimental models we have studied—EAE, EAT, and AA—are all influenced greatly by genes within and without the MHC. Not all rats and mice immunized with BP, Tg, or MT express disease. Similarly, autoimmune disease is not an inevitable outcome of the genome alone. For example, about 50% of monozygotic twins escape developing insulin-dependent diabetes mellitus, even when they have grown up in the same house as have their genotypically identical siblings who require insulin. Some environmental factor is needed to induce the disease. Viewed from this aspect, perhaps induced models of autoimmunity such as AA are more faithful to the human condition than are the more spontaneous models such as mouse lupus erythematosus which is inevitable in almost every mouse in a specially bred population. Thus, there is no reason to disqualify experimental models of disease merely because we know how they can be triggered.

Some instances of autoimmunity in humans have been associated with microbial infection: Reiter's syndrome, acute rheumatic fever, ankylosing spondylitis, diabetes, and rheumatoid arthritis are examples. Lines of T lymphocytes derived from patients might be used, as we have done in AA, to uncover molecular mimicry between microbial antigens and tissue-specific epitopes [32]. Multiple sclerosis probably involves autoimmunity to an unidentified component of CNS white matter. The isolation of T lymphocyte lines from patients could provide a way of characterizing the critical target antigen. For example, we have found that lines of T lymphocytes from rats with EAE regularly show specificity for the major encephalitogenic fragment of BP, even if we use crude white matter to select the lines (unpublished data). Thus, T lymphocyte lines can be used to identify the immunologically dominant epitopes within an undefined mixture of substances.

Beyond diagnosis, could T lymphocyte lines or clones be used to manipulate disease? Obviously, treatment rather than prevention is the goal. The value of the animal experiments derives from the observation that this goal is feasible. How it can be done in humans and whether success will outweigh the risks remains to be seen. The studies described here provide an outline for beginning the work.

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